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ANALGESICS AND CANCERS OF THE RENAL PELVIS AND URETER

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To evaluate renal pelvis and ureter (RPU) cancer risk in relation to lifetime use of analgesics, a population-based case-control study was carried out in 3 areas of the United States. Among 502 cases and 496 controls diagnosed and interviewed during 1983–1986, no significant increases in risk were found for any of the non-prescription and prescription analgesics evaluated or among regular users of phenacetin, acetaminophen or aspirin. Neither cumulative lifetime ingestion nor duration of regular use of these 3 drugs, whether alone or in combination, was associated with significantly increased risk of RPU cancer, although a slight excess was observed among long-term users of acetaminophen. Risk was not increased among persons reporting highest cumulative dose and/or longest duration of phenacetin use. Although our study of RPU cancer is the largest to date, it was nonetheless limited by the small number of regular analgesic users and the relatively low response rates. Because of the relatively recent onset of widespread use of acetaminophen, its pharmacologic similarity to phenacetin, a known urothelial carcinogen, and the elevation in risk seen in long-term users, further surveillance of this analgesic is warranted.

Although cancers of the renal pelvis and ureter (RPU) are relatively rare, their incidence has increased in the United States approximately 3% per year since 1970 (Devesa *et al.,* 1990). Case-control studies have generally shown elevated risks associated with cigarette smoking, and with prior use of analgesics (McCredie *et al.,* 1982, 1983*a,b,* 1993; McLaughlin *et al.,* 1983, 1992; McCredie and Stewart, 1988; Jensen *et al.,* 1989; Ross *et al.,* 1989). Phenacetin has been implicated in most studies (McCredie *et al.,* 1982, 1983*a,b,* 1993; McLaughlin *et al.,* 1983; McCredie and Stewart, 1988; Jensen *et al.,* 1989) but not all (Ross *et al.,* 1989). One study has linked RPU cancer with aspirin (Ross *et al.,* 1989), while others have found associations with combinations of phenacetin and aspirin (McCredie *et al.,* 1993). Acetaminophen, as a single drug or in compound form, gained widespread popularity beginning in the mid-1970s as phenacetin products became less available and were then withdrawn. In the early 1980s, use of acetaminophen increased further after reports of an association between salicylate use and Reye's syndrome (Starko *et al.,* 1980). In 3 case-control studies, non-significant increased risks of RPU cancer have been reported among persons using acetaminophen alone (McCredie *et al.,* 1993) or with phenacetin (McLaughlin *et al.,* 1983; Ross *et al.,* 1989). To further examine the carcinogenic risks of analgesic drugs, we carried out a large population-based case-control study of RPU cancer.

MATERIAL AND METHODS

Methods for this study have been described elsewhere (McLaughlin *et al.,* 1992) and are briefly summarized here. Cases of histologically confirmed RPU cancers diagnosed between January 1, 1983 and December 31, 1986 were identified from population-based cancer registries in New Jersey, Iowa and Los Angeles among persons aged 20–79 years. The study was restricted to whites because few cases of these rare neoplasms occurred among non-whites in the 3 geographic areas. Deceased cases were not included in the study. Controls for cases under age 65 at diagnosis were chosen using random digit dialing, while controls for cases aged 65 and older were selected from Medicare files maintained by the Health Care Financing Administration. In each geographic area, controls were frequency-matched to cases by age (5-year groups) and gender.

Trained interviewers, blinded to case-control status, carried out in-person structured interviews in the homes of subjects. Next of kin of deceased cases were not interviewed because these respondents would be unlikely to provide accurate estimates of lifetime use for over-the-counter analgesics. A detailed, comprehensive list of questions was asked about lifetime use of more than 50 over-the-counter and prescription analgesics, excluding the 5-year period prior to interview. A booklet containing photographs of the analgesics and their packaging was used as an aid in recall of the many products, some of which were no longer on the market. For each analgesic, subjects were asked about ever use, regular use (defined as a minimum of 2 or more doses per week for at least 1 month or longer), age started and stopped, total duration of use and usual dose taken. In addition, the questionnaire sought information on demographics, tobacco use, medical history, other medications, diet, and occupation.

An analgesic ingredient matrix was developed by a pharmacist based on detailed research of pharmaceutical information sources that incorporated data about the constituents of analgesics dating back to the 1920s. Annual usage and amounts of specific constituents based on this matrix were estimated for each year of reported usage. For regular users, lifetime cumulative exposure to 3 major categories of analgesics (aspirin, acetaminophen and phenacetin) was estimated in kilograms during a subject's lifetime. Information on ibuprofen was not collected as it was not an over-the-counter product until 1984, which was only 2 years before data collection, thereby allowing insufficient latency for the evaluation of carcinogenic potential.

Because the number of non-users of analgesics among all subjects was small (12.6% of cases, 16.7% of controls) and the results for regular users *vs.* non-users were very similar to those for regular *vs.* non-regular users, we combined non-users and non-regular users (64.1% of cases, 57.7% of controls) into a single referent group (consisting of 385 or 76.7% of cases and 369 or 74.4% of controls).

Summary odds ratios (OR), adjusting for the effects of age, gender, geographic area and cigarette smoking (based on quartiles of pack–years derived from all controls), were calculated using the maximum likelihood method and 95% confidence intervals (CI; Breslow and Day, 1980).

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RESULTS

Of the 812 eligible cases, 502 (62%) were interviewed, including 308 (193 males, 115 females) with renal pelvis cancer and 194 (138 males, 56 females) with ureter cancer. Cases included 97% with transitional cell and 3% with squamous cell or papillary tumors not otherwise specified. Eligible cases not interviewed included 215 who had died or were too ill to participate, 95 who refused or whose physician denied permission to contact, 30 untraceable or moved, 14 due to a language problem and 59 other. Non-interviewed cases were slightly older but were otherwise similar to those interviewed in educational level and household income. The 496 controls (315 males, 181 females) represented 66% of those potentially eligible and ascertained from the Health Care Financing Administration and 54% from random digit dialing (representing a 92% response rate at the household screening phase [90% in New Jersey, 96% in Iowa and 91% in Los Angeles] and a 59% participation rate at the interview phase]. Eligible controls not interviewed included 146 refusals, 63 untraceable or moved, 31 deceased or too ill, 27 due to a language problem and 23 other.

There were 239 cases and 201 controls interviewed in New Jersey, 95 cases and 80 controls in Iowa and 168 cases and 215 controls in Los Angeles. Cases and controls were similar in age (median age for cases was 66, median for controls was 68) and educational levels (36.3% of cases *vs.* 37.9% of controls had completed at least 1 year of education subsequent to high school graduation).

Among all subjects, the most common reasons for ever use of analgesics were to ameliorate symptoms of a cold (48.7% of cases, 51.6% of controls) and to treat the pain of sore throats (32.1% of cases, 33.1% of controls). Approximately 2.3% of cases and 3.4% of controls used aspirin for prevention of heart attacks or strokes.

It was not possible to calculate risks for RPU cancer associated with use of most of the brand name analgesics among regular users due to small numbers, but among the few compounds with at least 5 or more regular users for both cases and controls, no significant associations were seen. Risks for renal pelvis and ureter cancer associated with the 3 major analgesic groups (phenacetin, acetaminophen and aspirin) were similar, despite the slightly higher median age at diagnosis of ureter (69 years) than renal pelvis (66 years) cancer. There were small differences in usage patterns by geographic area (*e.g.*, the highest proportion of cases and controls who had used specific analgesics 20 or more times or had greatest cumulative lifetime use was in Iowa and the lowest corresponding proportion in Los Angeles; data not shown). While women were estimated to have higher cumulative use than men for each of the 3 major analgesic groups, relative risks were similar by gender. Risk estimates are therefore reported for men and women together and for both renal pelvis and ureter cancers combined. Because of the limited numbers of subjects regularly using a particular brand name drug, the remainder of the analysis focuses on the 3 major categories.

Among cases and controls, similar proportions used phenacetin (6.0% of cases, 7.1% of controls), aspirin (13.7% of cases, 15.3% of controls) and acetaminophen (7.0% of cases, 6.2% of controls). Generally, no association was observed with use of each major type of analgesic, regardless of whether the drug was used alone or in combination with other analgesics (Table I).

Risk did not increase with greater duration of phenacetin or aspirin use, but a non-significant 40% increase in risk was observed with 10 or more years of regular use of acetaminophen (Table II). For all three major categories of analgesics, the median reported age at first use was a few years earlier for cases than controls, although there was substantial variation

TABLE I – RISKS OF RENAL PELVIS AND URETER CANCER ASSOCIATED WITH REGULAR[1] USE AND WITH LIFETIME EXPOSURE TO ONE DRUG ONLY OF MAJOR CATEGORIES OF ANALGESICS

Type of analgesic	Cases N	Cases (%)	Controls N	Controls (%)	Odds ratios[2]	95% Confidence intervals
No regular use	385	(76.7)	369	(74.4)	1.0	—
Regular use						
Any analgesic	117	(23.3)	127	(25.6)	0.8	0.6–1.1
Phenacetin	30	(6.0)	35	(7.1)	0.8	0.5–1.4
Acetaminophen	35	(7.0)	31	(6.2)	1.0	0.6–1.8
Aspirin	69	(13.7)	76	(15.3)	0.8	0.6–1.2
Other analgesics	35	(7.0)	39	(7.9)	0.8	0.5–1.3
Only use						
Phenacetin	1	(0.2)	2	(0.4)	0.5	0.0–6.0
Acetaminophen	9	(1.8)	9	(1.8)	0.8	0.3–2.3
Aspirin	33	(6.6)	36	(7.3)	0.8	0.5–1.3

[1]Regular use was defined as a minimum of 2 or more doses per week for at least 1 month or longer.–[2]Adjusted for age, gender, geographic site and cigarette smoking.

TABLE II – RISK OF RENAL PELVIS AND URETER CANCER ASSOCIATED WITH DURATION OF USE OF MAJOR CATEGORIES OF ANALGESICS

Type of analgesic	Number of cases	Number of controls	Odds ratios[1]	95% Confidence intervals
No regular use	385	369	1.0	—
Phenacetin				
≤4 yr	12	16	0.7	0.3–1.6
5–9 yr	6	6	0.8	0.3–2.7
≥10 yr	11	13	0.9	0.4–2.2
Acetaminophen				
≤4 yr	13	12	0.9	0.4–2.0
5–9 yr	10	10	1.0	0.4–2.5
≥10 yr	9	7	1.4	0.5–4.1
Aspirin				
≤4 yr	20	19	1.0	0.5–1.9
5–9 yr	6	13	0.4	0.1–1.0
≥10 yr	41	44	0.9	0.5–1.4
Any[2]				
≤4 yr	24	26	0.9	0.5–1.6
5–9 yr	13	17	0.6	0.3–1.4
≥10 yr	43	45	0.9	0.5–1.4

[1]Adjusted for age, gender, geographic site and cigarette smoking.–[2]Includes phenacetin or acetaminophen or aspirin.

TABLE III – RISK OF RENAL PELVIS AND URETER CANCER ASSOCIATED WITH CUMULATIVE LIFETIME USE OF MAJOR CATEGORIES OF ANALGESICS

Type of analgesic	Number of cases	Number of controls	Odds ratios[1]	95% Confidence intervals
No regular use	385	369	1.0	—
Phenacetin				
≤ 1.0 kg	21	23	0.8	0.4–1.6
> 1.0 kg	9	12	0.8	0.3–2.1
Acetaminophen				
≤ 1.0 kg	22	17	1.1	0.5–2.1
> 1.0 kg	13	14	1.0	0.4–2.3
Aspirin				
< 1.0 kg	31	29	1.0	0.6–1.7
1.0–5.0 kg	20	28	0.6	0.3–1.1
> 5.0 kg	18	19	0.9	0.5–1.9

[1]Adjusted for age, gender, geographic area and cigarette smoking.

within both groups. The median interval between last use and the interview was the same for cases and controls taking acetaminophen or aspirin, but for phenacetin the interval was 18 years for cases and 20 years for controls. There was no evidence that persons who last used phenacetin within 18 years of interview had higher risks of RPU cancer than those who last used this analgesic 18 or more years prior to interview (data not shown).

No dose-response relationship was observed between cumulative lifetime ingestion and risk of RPU cancer for any of the 3 analgesic groups. However, the number of subjects reporting detailed quantitative information was small (Table III).

DISCUSSION

This multi-center, population-based case-control study of RPU cancer in the United States revealed no significant increase in risk among women or men who regularly used analgesics. In addition, risk was not significantly associated with cumulative dose or duration of use. Despite the large number of subjects, our study was hampered by the low proportion of regular analgesic users and the lack of "analgesic (particularly phenacetin) abusers", the latter demonstrated by the virtual absence of subjects with an estimated cumulative lifetime dose of 5 kg or more of phenacetin and/or a history of analgesic nephropathy. Still, it was possible to evaluate associations with 3 major categories of analgesic agents.

Phenacetin

Phenacetin was first implicated in clinical series of renal pelvis tumors 3 decades ago and continued to be linked with renal pelvis and ureter cancers in subsequent reports from Scandinavia, Australia and other areas with a high prevalence of analgesic use (reviewed by McCredie, 1993). Although phenacetin has been recognized as a urothelial carcinogen, it appears that up to 80% of this agent is metabolized to acetaminophen, which is excreted in the urine as glucuronide and sulfate conjugates (Hinson, 1983; Hiraga and Fujii, 1985). Whatever the proximal carcinogen, heavy users of phenacetin-containing analgesics have shown elevated risks not only for cancers of the renal pelvis and ureter (McCredie *et al.,* 1982, 1983*a,b;* McLaughlin *et al.,* 1983; McCredie and Stewart, 1988; Jensen *et al.,* 1989) but also the bladder (Piper *et al.,* 1986). As a result of the epidemiologic evidence, phenacetin-containing mixtures have been designated as carcinogenic for transitional cell tumors of the renal pelvis, ureter and bladder (IARC, 1987). Experimental evidence has suggested that phenacetin may act as a promoter in view of its potential to induce urothelial hyperplasia (Bach, 1993) and to promote the development of renal pelvis tumors when used in conjunction with a urinary tract carcinogen (Anderstrom *et al.,* 1983).

It is noteworthy that most case-control studies linking phenacetin to urinary tract tumors were carried out during the 1970s, when many phenacetin-containing preparations were still widely used, and reported use reflected consumption from the 1950s and 1960s. In contrast, during the period 1983–1986, when cases were diagnosed in our study, phenacetin products had been off the market for a decade or more, following recognition of its nephrotoxic and carcinogenic effects.

The inability of our study to detect an association between phenacetin and RPU cancer is not surprising given the low lifetime prevalence of regular use (6–7%) reported by the study population and the lack of abusers based on cumulative estimated lifetime use. Another reason for our inability to demonstrate an association between phenacetin-containing analgesics with RPU cancer is the relatively low prevalence of analgesic abuse in the United States compared with countries like Australia and Switzerland (Murray and Goldberg, 1978; McCredie, 1993).

The reported prevalence of use is likely to become even lower in future studies, since phenacetin products were generally unavailable in the United States and elsewhere as over-the-counter medications during the 1970s and were then withdrawn from the market completely in 1983 (Federal Register, 1983). Another feature complicating the interpretation of the findings is that phenacetin was rarely available as a single agent but was generally combined with other drugs, including aspirin and codeine (McCredie, 1993). To some extent, the absence of an association may also reflect poor recall of analgesics used more than a decade prior to interview, as well as telescoping more recent usage patterns to the past (Bradburn *et al.,* 1987). In addition, the lack of association may have been influenced by the relatively low response rates, especially if non-regular users were more likely to refuse participation as controls or if cases who regularly used analgesics had shorter survival.

Acetaminophen

Neither regular, sole nor cumulative use of acetaminophen was associated with an elevated risk of RPU cancer in our study, but long-term users had a non-significant 40% increase in risk. Acetaminophen is available either as a single drug or in compound preparations (*e.g.,* with codeine), and it became increasingly popular as an alternative to aspirin beginning in the mid-1970s. However, concerns about acetaminophen have been raised since it is the primary metabolite produced by phenacetin (Hinson, 1983). In addition, 2 prior case-control studies in the United States revealed non-significant 4-fold excesses of renal pelvis cancer among persons using acetaminophen and/or phenacetin (McLaughlin *et al.,* 1983; Ross *et al.,* 1989), while an Australian study recently reported an association between acetaminophen and renal pelvis cancer (McCredie *et al.,* 1993). An earlier study in Australia found a link

with ureter cancer but not renal pelvis or bladder cancer (McCredie and Stewart, 1988). However, these studies could not disentangle the risk associated with phenacetin *vis-a-vis* acetaminophen due to the small numbers involved and overlapping consumption. Because of the relatively recent widespread usage of acetaminophen, it may be too soon to determine whether or not this analgesic is related to cancers of the urinary tract. To date, the results of bioassay studies have not shown consistent evidence for an association (National Toxicology Program, 1993).

Aspirin

We found no excess risk of RPU cancer associated with regular or cumulative use of aspirin as a single agent or combined product. Some earlier studies reported an elevated risk of RPU cancer associated with aspirin use in Denmark (Jensen *et al.,* 1989) and Los Angeles (Ross *et al.,* 1989), although the Danish investigators attributed their finding to concomitant use of phenacetin and the Los Angeles study results were not adjusted for cigarette smoking.

Comment

Among the strengths of the present case-control study was the large sample size when compared with earlier studies, the exclusion of subjects who could not directly participate in the interview, the detailed assessment of analgesic use by well-trained interviewers and the use of a sophisticated ingredient matrix developed for this study. However, there were 3 important limitations: *(i)* the preponderance of analgesic use was of over-the-counter products, which are often used intermittently, although difficulties in recall may be reduced by our emphasis on regular users; *(ii)* no alternative data sources were available to validate information obtained during personal interviews and *(iii)* exclusion of cases and controls who died or were too ill to be interviewed, along with refusals by some subjects or their physicians, resulted in a relatively low participation rate. Thus, interviewed cases probably had longer survival than non-participating cases, and some cases may have been excluded with medical conditions requiring greater use of analgesics.

In summary, this population-based case-control study of RPU cancer revealed no association with phenacetin use, despite previous reports of a causal relation, reflecting the discontinued use of this drug in the 1970s. There was no evidence of an elevated risk associated with aspirin use, in contrast to findings of an earlier study. Finally, a non-significant excess risk seen among long-term users of acetaminophen may suggest the need for continued surveillance of the long-term effects of this drug, which has been widely used since the mid-1970s.

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